Etiological Profile of Fever of Short Duration without Focus in Children Aged 1- 36 months

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CERTIFICATE

This is to certify that the dissertation titled**,"** ***Etiological Profile of Fever of Short Duration without Focus in Children aged 1- 36 months"*** submitted by **Dr.S.Sangeeth**, to the Faculty of Pediatrics, The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfillment of the requirements for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2009-2011.

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This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

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CONTENTS

Introduction

Febrile illnesses in infants and children account for 20% of paediatric visits.[1,2]Various set temperatures have been used to define fever, but commonly accepted definition for fever is temperature of > 38.08C (100.48F). This value derived from studies done by Wunderlich, who took 1 million measurements on 25,000 patients and proposed that this temperature was the upper limit ofnormal[3]. Though there is less invasive means of measuring temperature exist, such as axillary and aural thermometry, there is a difference in measurements exists.[4,5]it warrants using the current outpatient reference standard, rectal thermometry, when measuring temperatures in young children. An accurate temperature measurement is especially important if one chooses to use fever guidelines, because the implementation of these guidelines is initiated once a patient meets a certain temperature threshold.Fever occurs when infectious and non infectious process interacts with the host defence mechanism.

The pattern of temperature changes may occasionally hint at the diagnosis:

- Continuous fever: Temperature remains above normal throughout the day and does not fluctuate more than 1 °C in 24 hours, *e.g.*lobar pneumonia, typhoid, urinary tract infection, brucellosis, or typhus.

Typhoid fever may show (*Wunderlich curve* of typhoid fever), with a slow stepwise increase and a high plateau. (Drops due to fever-reducing drugs are excluded.)

- Intermittent fever: The temperature elevation is present only for a certain period, later cycling back to normal, *e.g.*malaria, kala-azar, pyaemia, or septicemia.

- Following are its types
    - Quotidian fever, with a periodicity of 24 hours, typical of Malaria
    - Tertian fever (48 hour periodicity), typical of Malaria
    - Quartan fever (72 hour periodicity), typical of *Plasmodium malariae*.
- Remittent fever: Temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, *e.g.*, infective endocarditis.
- Pel-Ebstein fever: A specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on. However, there is some debate as to whether this pattern truly exists.[6]

Body temperature is regulated by thermo sensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature as well as cold and warm receptors located in skin and muscles. A trigger of the fever, called a pyrogen causes a release of prostaglandin E2 (PGE2). PGE2 then in turn acts on the hypothalamus, which generates a systemic response back to the rest of the body, causing heat-creating effects to match a new temperature level.

In many respects, the hypothalamus acts like a thermostat.[7]When the set point is raised, the body rises its temperature by both active generation of heat and retaining heat. Vasoconstriction causes reduction in heat loss through the skin and person to feel cold. If these are insufficient to make the blood temperature in the brain match the new setting in the hypothalamus, then shivering produce more heat by muscle movements. once fever stops, and the hypothalamic setting is set lower; the reverse of these processes (vasodilation, end of shivering and non shivering heat production) and sweating are used to cool the body to the new, lower setting.

A pyrogen is a substance that induces fever. These can be either internal (endogenous) or external (exogenous) to the body. Major endogenous pyrogens are interleukin 1 (α and β),[8] interleukin 6 (IL-6) and tumor necrosis factor-alpha. Minor endogenous pyrogens include

interleukin-8, tumor necrosis factor-α, tumor necrosis factor-β, macrophage inflammatory protein-α and macrophage inflammatory protein-β as well as interferon-α, interferon-β, and interferon-γ.[8]Some substances produced within the body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen-antibody complexes in the presence of complement, complement components, lymphocyte products, bile acids, and androgenic steroid metabolites.[15]

The bacterial substance lipopolysaccharide (LPS), present in the cell wall of some bacteria, is an example of an exogenous pyrogen. Pyrogenicity may vary: In extreme examples, some bacterial pyrogens known as superantigens can cause rapid and dangerous fevers. In essence, all endogenous pyrogens are cytokines, molecules that are a part of the innate immune system. They are produced by phagocytic cells and cause the increase in the thermoregulatory set-point in the hypothalamus.

Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drugs. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol. Along with infectious diseases and drugs, malignancy and inflammatory diseases can cause fever through the production of endogenous pyrogens.[16]

Heat production exceeding heat loss is the second mechanism that leads to fever, with examples including salicylate poisoning and malignant hyperthermia. Defective heat loss is the third mechanism of fever genesis, for example, in children with ectodermal dysplasia or victims of severe heat exposure

There are arguments for and against the usefulness of fever, In theory, fever can aid in host defense. There are some important immunological reactions that are speed up by temperature, and some pathogens with strict temperature preferences could be suppressed. Research has demonstrated that fever has several important functions in the healing process:

- Increased mobility of leukocytes
- Enchanced leukocytes phagocytosis
- Endotoxin effect decreasedIncreased
- proliferation of leukocytes

The management of the febrile young child continues to evolve. Epidemiology of bacterial infections varies considerably. In united states Haemophilus influenza which was previously presented as significant pathogen resulting in substantial morbidity and mortality in young children. Haemophilus influenza was of all positive cultures 19% of

febrile children who presented to a pediatric walk-in clinic in 1972[9], but after Hemophilus influenzae type b vaccine the epidemiology of invasive bacterial disease changed dramatically. H influenzae type b has been almost eliminated with a 94% decline in H influenzae meningitis shortly afterthe introduction of the Hib vaccine.[10,11] Combining the results of two largest studies of occult bacteremia in patients seen in the mid 1990s in Boston and Philadelphia, no blood cultures grew H. influenzae from 15,366patients.

Differential diagnosis of fever is quite broad and includes both infectious and noninfectious causes,[12] the most of febrile children have underlying infectious causes of fever. Diagnostic strategies stress the detection of bacterial disease since bacterial diseases are more likely to be associated with worse outcomes, but even viral infections can also be associated with significant morbidity and mortality, especially in younger children.

Fever in children may be categorised as

1. Fever due to infection without Focus (no rash)
2. Fever with localised sign (no rash)
3. Fever with rash.

Fever without a focus refers to a rectal temperature of 38^{o}C or higher as the sole presenting feature. The terms “fever without localizing

signs" and "fever of unknown origin" (FUO) are subcategories of fever without a focus.

The majority of these children who present with fever are younger than 3 years. Most children have an apparent source of infection (ie, a viral respiratory infection, acute otitis media, or enteritis). Both minor and life threatening infectious diseases, including viral respiratory infections and bacterial meningitis are most common in this age group. However, in 20% of the cases[1], the paediatrician may not able to identify focus of the infection by the patient's clinical history and detailed clinical examination. This is called fever without source (FWS).[13,14]

Occult bacteremia (bacteremia without an apparent infection) occurs in 1.5% of relatively well-appearing children between 1-36 mo of age with fever. Without treatment occult bacteremia may subside spontaneously with sequelae, may persist or may lead to localized infections, such as meningitis, pneumonia, cellulites, or suppurative arthritis. The pattern of sequelae may be related to host factors and the offending organism. In some children, the occult bacteremic illness can represent the early signs of serious localized infection rather than a transient disease state.

Fever without Localizing Signs

Fever of acute onset, with duration of <1 wk and without localizing signs, is a common diagnostic dilemma in children <36 mo of age. The aetiology and evaluation of fever without localizing signs depends on the age of the child. Usually three 3 age groups are considered: neonates or infants to 1 mo of age, infants >1 month to 3 month of age, and children >3 month to 3 year of age. Many guidelines were published to aid in evaluating the healthy 0 to 36 mo old with fever without a source. But after the use of conjugate *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* vaccines, the rates of infections with these 2 pathogens have decreased dramatically[17]. As a result modifications of the 1993 guidelines have been advocated. Children in high-risk groups need to be treated aggressively.

FEBRILE PATIENTS AT INCREASED RISK FOR SERIOUS BACTERIAL INFECTIONS[18]

RISK GROUP	DIAGNOSTIC CONSIDERATIONS
IMMUNOCOMPETENT PATIENTS	
Neonates (<28 days)	Sepsis and meningitis caused by group B streptococcus, *Escherichia coli, Listeria monocytogenes*; neonatal herpes simplex virus infection,

RISK GROUP	DIAGNOSTIC CONSIDERATIONS
	enteroviruses
Infants 1to3 mo	Serious bacterial disease occurs in 10-15%, including bacteremia in 5%; urinary tract infection
Infants and children 3 to 36 mo	Occult bacteremia in <0.5% of children immunized with both *Haemophilus influenzae* type b and pneumococcal conjugate vaccines; urinary tract infections
Hyperpyrexia (>40^{o}C)	Meningitis, bacteremia, pneumonia, heatstroke, hemorrhagic shock-encephalopathy syndrome
Fever with petechiae	Bacteremia and meningitis caused by *Neisseria meningitidis*, *H. influenzae* type b, and *Streptococcus pneumoniae*
IMMUNOCOMPROMISED PATIENTS	
Sickle cell disease	Sepsis, pneumonia, and meningitis caused by *S. pneumoniae*, osteomyelitis caused by *Salmonella* and *Staphylococcus aureus*

RISK GROUP	DIAGNOSTIC CONSIDERATIONS
Asplenia	Bacteremia and meningitis caused by *N. meningitidis, H. influenzae* type b, and *S. pneumonia*
Complement or properdin deficiency	Sepsis caused by *N. meningitides*
Agammaglobulinemia	Bacteremia, sinopulmonary infections
AIDS	*S. pneumoniae, H. influenzae* type b, and *Salmonella* infections
Congenital heart disease	Infective endocarditis; brain abscess with right-to-left shunting
Central venous line	*Staphylococcus aureus*, coagulase-negative staphylococci, *Candida*
Malignancy	Bacteremia with gram-negative enteric bacteria, *S. aureus*, and coagulase-negative staphylococci; fungemia with *Candida* and *Aspergillus*

Neonates

Neonates with fever without focus are greatest challenge to evaluate because of limited signs of infection, making it difficult to clinically differentiate between a serious bacterial infection and self-limited viral illness. Immaturity of the immune responses in first few months of life also increases the significance of fever in the young infant. In neonates with fever and do not appear ill have a 7% risk of having a serious bacterial infection. Although neonates can have community acquired infection, they are mainly at risk for late-onset neonatal bacterial diseases (group B streptococci, *Escherichia coli,* and *Listeria monocytogenes*) and perinatally acquired herpes simplex virus (HSV) infection.

Practice guidelines recommend that if a neonate who had fever recorded at home by a reliable parent, the patient must be considered as a febrile neonate. Because of unreliable physical findings and the presence of an immature immune system, all febrile neonates should be hospitalized; blood, urine, and cerebrospinal fluid (CSF) should be cultured. Child should be given empirical intravenous antibiotics. CSF studies should include cell counts, glucose and protein levels, Gram stain, and culture; HSV and entero virus polymerase chain reaction should be considered. Stool culture and chest radiograph also to be done as the part of the

evaluation. Combination of antibiotics such as ampicillin and cefotaxime are recommended. Acyclovir should be included if HSV infection is suspected owing to the presence of CSF pleocytosis or known maternal history of genital HSV, especially at the time of delivery.

1 Month to 3 Months

Majority of the children with fever without localizing signs in the age group of 3-12 months likely have a viral syndrome. In contrast to bacterial infections, viral diseases may have a distinct seasonal pattern: respiratory syncytial virus and influenza A virus infections commonly seen during the winter. Enterovirus infections usually occur in the summer and fall. Although a viral infection is the most likely etiology, fever in these children should always suggest the possibility of serious bacterial disease. Organisms may include group B streptococcus, *L.monocytogenes*, *Salmonella enteritis*, *E. coli*, *Neisseria meningitidis*, *S. pneumoniae,* Hemophilus influenza and *Staphylococcus aureus*. Pyelonephritis is common in uncircumcised infant boys and infants with urinary tract anomalies. Other potential bacterial diseases include otitis media, pneumonia, omphalitis, mastitis, and other skin and soft tissue infections.

Ill-appearing (toxic) febrile infants ≤3 mo of age should be hospitalised and immediate parenteral antimicrobial therapy after cultures of blood, urine, and CSF are obtained. Ampicillin to cover *L. monocytogenes* and enterococcus) plus either ceftriaxone or cefotaxime is an initial antimicrobial regimen for ill-appearing infants in this age group. This regimen is effective against the usual bacterial pathogens causing sepsis, urinary tract infection, and enteritis in young infants. However, if meningitis is suspected because of CSF abnormalities, vancomycin should be included to treat possible penicillin-resistant *S. pneumoniae* until the results of culture and susceptibility tests are known.

Many academic institutions have studied the optimal management of low-risk patients in this age group with fever without a focus. The use of viral diagnostic studies (enteroviruses, respiratory viruses, rotavirus, and herpesvirus) in combination with the Rochester Criteria or similar criteria can enhance the ability to determine which infants are at high risk for serious bacterial infections. In Febrile infants where a virus has been detected are at low or no risk of a serious bacterial infection. Well-appearing infants 1-3 mo of age can be managed using low-risk laboratory and clinical criteria and if reliable parents are involved and close follow-up is assured.

LOW RISK CRITERIA IN 1-3 MONTHS OLD WITH FEVER[18]

BOSTON CRITERIA
Infants are at low risk if they appear well, have normal physical examination, have a caretaker reachable by telephone, and laboratory tests are as follows:
• CBC: <20,000 WBC/mm^3 • Urine: negative leukocyte esterase • CSF: leukocyte count less than 10 x10^6/L,
PHILADELPHIA PROTOCOL
Infants are at low risk if they appear well, have a normal physical examination, and laboratory tests are as follows:

- CBC: <15,000 WBC/mm^3; band: total neutrophil ratio <0.2
- Urine: <10 WBC/HPF; no bacteria on Gram stain
- CSF: <8 WBC/mm^3; no bacteria on Gram stain
- Chest radiograph: no infiltrate
- Stool: no RBC; few to no WBC

PITTSBURGH GUIDELINES

Infants are at low risk if they appear well, have a normal physical examination, and laboratory tests are as follows:

- CBC: 5,000-15,000 WBC; peripheral absolute band count <1500/mm^3
- Urine (enhanced urinalysis): 9 WBC/mm^3 and no bacteria on Gram stain
- CSF: 5 WBC/mm^3 and negative Gram stain; if bloody tap, then WBC : RBC $\leq$ 1 : 500
- Chest radiograph: no infiltrate
- Stool: 5 WBC/HPF with diarrhea

ROCHESTER CRITERIA
Infants are at low risk if they appear well, have a normal physical examination, and laboratory findings are as follows:
• CBC: 5,000-15,000 WBC/mm^3; absolute band count ≤1500/mm^3 • Urine: <10 WBC/HPF at 40x • Stool: <5 WBC/HPF if diarrhea

Infants 1-3 mo of age with fever who appear generally well; who have been previously healthy; who have no evidence of skin, soft tissue, bone, joint, or ear infection; and who have a peripheral white blood cell (WBC) count of 5,000-15,000 cells/mm^3, an absolute band count of <1,500 cells/mm^3 and normal urinalysis and negative culture (blood and urine) results are unlikely to have a serious bacterial infection. The negative predictive value with 95% confidence of these criteria for any serious bacterial infection is >98% and for bacteremia is >99%. Among serious bacterial infections, pyelonephritis is the most common and may be seen in well-appearing infants who have fever without a focus or in those who appear ill. Urinalysis may be negative in infants <2 mo of age with pyelonephritis. Bacteremia may be present in <30% of infants with pyelonephritis.

The decision to obtain CSF studies in the well-appearing 1-3 mo old infant depends on the decision whether to administer empirical antibiotics or not. A lumbar puncture may be deferred. When close observation planned without antibiotics. If the child deteriorates clinically, a full sepsis evaluation should be performed, and intravenous antibiotics should be administered. When empirical antibiotics are initiated, CSF studies should be obtained, preferably before administering antibiotics.[20]

3 Months to 36 Months of Age

Nearly 30% of febrile children in the 3-36 mo age group have no localizing signs of infection. Viral infections are the major cause of fevers in this population, but serious bacterial infections do occur and are caused by the same pathogens listed for patients 1-3 mo of age, except those acquired perinatally, *S. pneumoniae*, *N. meningitidis*, and *Salmonella* account for most cases of occult bacteremia. Hib was an important cause of occult bacteremia in young children before universal immunization with conjugate Hib vaccines and remains common in underdeveloped countries that have not implemented these vaccines.

Risk factors for increased probability of occult bacteremia include temperature $\geq 39^{o}C$, WBC count $\geq 15{,}000/mm^3$, and elevated absolute

neutrophil count, band count, erythrocyte sedimentation rate, or C-reactive protein. The incidence of bacteremia and /or pneumonia or pyelonephritis, among infants 3-36 mo of age increases as the temperature (especially >40^{o}C) and WBC count (especially >25,000) increase[19]. However, no combination of laboratory tests or clinical assessment is accurate in predicting the presence of occult bacteremia. Socioeconomic status, race, sex, and age (within the range of 3-36 mo) do not appear to affect the risk for occult bacteremia.[19]

In some children, the occult bacteremic illness can represent the early signs of serious localized infection rather than a transient disease state. Hemophilus bacteremia is characteristically associated with a higher risk for localized serious infection than is bacteremia due to *S. pneumoniae.* Hospitalized children with Hemophilus bacteremia often develop focal infections, such as meningitis, epiglottitis, cellulitis, pericarditis, or osteoarticular infection, and spontaneous resolution of bacteremia is rare. In patients with pneumococcal bacteremia (occult or focal), spontaneous resolution occurs in 30-40%, with a higher rate of spontaneous resolution among well-appearing children.

Important bacterial infections among children 3-36 mo of age with localizing signs include otitis media, sinusitis, pneumonia (not always

evident without a chest x-ray), enteritis, urinary tract infection, osteomyelitis, and meningitis.

Treatment of toxic-appearing febrile children 3-36 mo of age who do not have focal signs of infection includes hospitalization and prompt institution of antimicrobial therapy after specimens of blood, urine, and CSF are obtained for culture. Consensus practice guidelines published in 1993 recommended that children 3-36 mo of age who have a temperature of <39C and do not appear toxic be observed as outpatients without performing diagnostic tests or administering antimicrobial agents. For non toxic-appearing infants with a rectal temperature of ≥39^{o}C, options include obtaining a blood culture and administering empirical antibiotic therapy (ceftriaxone, a single dose of 50 mg/kg, not to exceed 1 g); if the WBC count is >15,000/mm^{3}, obtaining a blood culture and beginning empirical antibiotic therapy; or obtaining a blood culture and observing as outpatients without empirical antibiotic therapy, with return for re-evaluation within 24 hr.

Guidelines for managing febrile children 3-36 mo of age who have received both Hib and *S. pneumoniae* conjugate vaccines have not been established, but careful observation without empirical administration of antibiotic therapy is generally prudent. Since fully vaccinated young children are at a much lower risk of occult bacteremia and meningitis as

the cause of acute fever without localizing signs, some advocate that the only laboratory tests needed in this age group when temperature is >39°C are a urinalysis and urine culture for circumcised boys <6 mo of age and uncircumcised boys and all girls <24 mo of age. Regardless of the management option the family should be instructed to return immediately if the child's condition deteriorates or new symptoms develop.

MANAGEMENT OF FEVER WITHOUT LOCALIZING SIGNS[18]

GROUP	MANAGEMENT
Any toxic-appearing child 0-36 mo and temperature ≥38°C	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child <1 mo and temperature ≥38°C	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child 1-3 mo and temperature ≥38°C	Two-step process **1** Determine risk based on history, physical examination, and laboratory studies.

GROUP	MANAGEMENT

	Low risk:
	• Uncomplicated medical history
	• Normal physical examination
	• Normal laboratory studies
	  • Urine: negative leukocyte esterase, nitrite and <10 WBC/HPF
	  • Peripheral blood: 5,000-15,000 WBC/mm^3; <1,500 bands or band : total neutrophil ratio <0.2
	  • Stool studies if diarrhea (no RBC and <5 WBC/HPF)
	  • CSF cell count (<8 WBC/mm^3) and negative Gram stain
	  • Chest radiograph without infiltrate
	2 If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in

GROUP	MANAGEMENT
	24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated.
Child 3-36 mo and temperature 38-39°C	Reassurance that diagnosis is likely self-limiting viral infection, but advise return with persistence of fever, temperatures >39°C, and new signs and symptoms
Child 3-36 mo and temperature >39°C	Two-step process: **1** Determine immunization status **2** If received conjugate pneumococcal and *H. influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys

GROUP	MANAGEMENT
	<6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines

Empirical antibiotic therapy in well-appearing children <36 mo of age who have not received Hib and *S. pneumoniae* conjugate vaccines and who have a rectal temperature of >39^{o}C and a WBC count of >15,000/mm^{3} is strongly recommended. If blood cultures are obtained and *S. pneumoniae* is isolated from the blood, the child should return to the physician as soon as possible after the culture results are known. If the child appears well, is afebrile, and has a normal physical exam, a second blood culture should be obtained and the child should be treated with 7-10 days of oral antimicrobial therapy. If the child appears ill and continues to have fever with no identifiable focus of infection at the time of follow-up, or if *Hemophylus . influenzae,* or *N. meningitidis* is present in the initial blood culture, the child should have a repeat blood culture,

be evaluated for meningitis (including lumbar puncture), and receive treatment in the hospital with appropriate intravenous antimicrobial agents. If the child develops a localized infection, therapy should be directed toward the likely pathogens

Review of literature

Fever without localising sign;

Although incidence of the cause of the fever in children may vary, most investigators found that infections predominate in this age group. Among the infections viral illness predominates.

B. M. Machado et al[21]conducted prospective study on 251 children and, of these, 215 were followed up until the final diagnosis. Toxemia was present in 20 children, and 195 were well-appearing (30 up to 3 months old and 165 from 3 to 36 months old). Among thosechildren from 3 to 36 months without toxemia, 95 had axillary temperature > 39 ºC. In 107 (49.8%) children, spontaneous resolution of fever; in 88 (40.9%), benign self-limited disease was identified; and in 20 (9.3%), had SBI. Among the cases of SBI, they identified 16 cases of urinary tract infections, three cases of pneumonia and one occult bacteremia. Conclusion: They concluded that guideline was shown to be appropriate to follow up these children using simple laboratory tests that can be carried out at most health facilities. The most frequent SBI in this sample was urinary tract infection.

Robert H. et a[22]l in a Prospective cohort study studied 3066 infants aged 3 months or younger with temperatures of at least 38°C. The PROS

clinicians hospitalized 36% of the infants, performed laboratory testing in 75%, and initially treated 57%with antibiotics. The majority (64%) were treated exclusively outside of the hospital. Bacteremia was detected in 1.8% of infants (2.4% of those tested) and bacterial meningitis in 0.5%. Well-appearing infant's aged 25 days or older with fever of less than 38.6°C had a rate of 0.4% for bacteremia/bacterial meningitis. Frequency of other illnesses included urinary tract infection, 5.4%; otitis media, 12.2%; upper respiratorytract infection,25.6%; bronchiolitis,7.8%; and gastroenteritis,7.2%. Conclusions : Pediatric clinicians in the United Statesuse individualized clinical judgment in treating febrile infants. In this study, relying on current clinical guidelines would not have improved care but would have resulted in more hospitalizations and laboratory testing.

Vinchurkar S[23]who studied 102 children in baoda in 2002 between the ages 0 and 36 months in 2002.37 (36.2 percent) out of 102 had bacterial infection, while 65 (63.8 percent) had non-bacterial illness. Staph.Aureus was the common aetiologic agent identified in blood culture.

Z. Nademi el al [24]studied One hundred and forty one children in between 8 days and 16 years of age were studied, 64% male, 55% aged under 2 years. Eighty three percent had of children had temperatures between 38 and 39°C. Twenty nine percent (41/141) had serious disease

but microbiologically or radiologically proven in only 22% (31/141); pneumonia (nine), meningitis (seven), sepsis (five), urinary tract infection (five), brain abscess (two), toxic shock syndrome (one), appendicitis (one), ischiorectal abscess (one). Forty two percent (5/12) of microbiologically proven meningitis and sepsis and 36% (8/22) of all meningitis and sepsis were due to meningococcal. Seventy one percent had non-serious diseases. In cases of serious disease the temperature was >39°C in 15% (sensitivity: 14%, specificity: 82%, PPV: 25%). Poor feeding and restlessness predicted serious disease with a sensitivity of 78% and 76%, respectively. Full blood count (FBC) was taken in 50% of patients on admission; in 44% of serious and 24% of non-serious diseases WBC was between 5000 and 15 000/mm^3 and WBC ≥15 000/mm^3 was seen in 39% of serious diseases (sensitivity:10%, specificity: 95%, PPV: 44%).*Conclusions*: One out of three of children referred with fever had a serious disease. Degree of temperature and WBC count were poor predictors of serious disease. Interestingly, poor feeding and restlessness were more sensitive predictors, suggesting high fever and WBC count cannot replace clinical assessment of the child with a temperature.

George O. Akpede,[25]conducted a prospective study in Six-hundred-and-forty-two previously healthy children aged 1 month to 5 years with fever of acute onset, without localizing signs of infection, over 1 year.

Sixty-three per cent had malaria, 4 per cent bacteraemia, and 7 percent malaria and bacteraemia. Neither infection was identified in 27 per cent. Malaria was the predominant infection irrespective of season, temperature on presentation, or age (except under 6 months). Gram-negative bacteraemia was overall commoner than Grampositive bacteraemia. But *Staphylococcus aureus* was the single most common organism (43 per cent) in bacteremia. The prevalence of malaria increased with age while that of bacteraemia decreased with age ($P< 0.0005$). The prevalence of an identifiable infection increased with the temperature on presentation ($P< 0.025$). conclusion: although malaria is the predominant infection in previously healthy under-5 children with acute fever without specific localizing signs of infection, bacteraemia (alone or associated with malaria) occur with an importantly high frequency. It is recommended that while presumptive treatment for malaria is justified in such children, evaluation for bacteraemia should be given consideration.

Richard et al [26]studied the prevalence of occult bacteremiain infants. Of 52 toxic infants involved in the study, an infectious source, commonly otitis media, was found in 26 (50%). Eighteen patients (35%) had WBC counts above 15,000. Bacteremia was documented in six patients (12%), due to *Streptococcus pneumoniae* in five and group C *Streptococcus* in one.

Walsh et al[27]Between September, 1996, and August, 1997, processed 2123 cultures. Of these, 365 (17.2%) grew a pathogen. Non-typhi salmonellae (NTS) and enteric Gram-negative bacilli constituted 67.4% of isolates, and *Streptococcus pneumoniae* constituted 16.4%. More than two-thirds of NTS episodes coincided with the peak malaria transmission season (January to June); 67% of bacteremic children were malnourished, 28% severely so. Screening tests for penicillin resistance suggested a rate of 21% among pneumococci. Conclusions: Bacteremia is common in hospitalized Malawian children and has a high mortality. There are high rates of resistance to some of the commonly used antibacterial agent

Patrick J Crocker[28] et al studied a selected series of febrile infants (N = 201) in an attempt to prospectively identify risk factors for bacteremia.. Twenty-one infants (9.5%) had positive blood cultures. WBC count of more than 15,000 correlated with bacteremia, with a sensitivity of 0.71 and a specificity of 0.73. The combination of fever higher than 39.4 C present for more than 12 hours and absolute polymorphonuclear count of more than 9,000 cells/mm^3 had a sensitivity of 0.62 and a specificity of 0.78 for bacteremia.

John E. MCGowan et al showed clinically important bacterial pathogens in the blood from 31 of 708 children in a three-month period. Diplococcus pneumoniae and *Haemophilusinfluenzae* were the most frequent of seven species identified. Bacteremia was most frequent in

children seven to 12 months old ($p<0.001$) and was associated with a white-cell count of 20,000 or more ($p<0.01$) and a temperature of 39.4°C or higher ($p<0.01$).

Morris CM,et al [29]conducted a prospective study to document the importance of urinary tract infection (UTI) as a cause of fever without a focus (FWF) in children less than 3 years of age. UTI was diagnosed on urine culture in 9 of the 98 children. Both urinary nitrite and leukocyte esterase tests were sensitive (89%) and specific (96%). Other causes of FWF were classified as non-specific viral infection (31 children), lower respiratory tract infection (11), malaria (7), meningitis (4), bacteraemia (1 neonate) and other or unknown causes. The finding of UTI in 9% of the children is consistent with data from other tropical countries.

Omolola O. Ayoolaet[30]et al studied 102 infants aged 1-12 month(s) attending the Children's Emergency Ward of University College Hospital, Ibadan,. Over38% of the infants had bacteraemia. *Escherichia coli* (35.9%), *Staphylococcus aureus*(33.3%), and *Klebsiella spp.*(10.3%*)* of positive cultures were commonly isolated. It is concluded that, age of ≤6 months, restlessness, and a white cell count of ≥15,000/mm3 are associated with a significantly increased risk of bacteraemia.

occul Shah, Sonal[31], studied 1866 patients 308 had no evidence of respiratory distress or lower respiratory tract findings and were studied for OP. Twenty-one patients had radiographic OP (6.8%; 95% confidence

interval [CI], 4.0%-10.6%).Conclusion: Occult pneumonia was identified in 1 of 15 patients undergoing CXR without respiratory distress or ausculatory findings. Obtaining a CXR for the detection of OP in children without cough and with fever for less than 1 day in duration should be discouraged

R.K. Kaushal et al [32]studied One hundred and thirty one children upto five years of age presenting with fever of >38ºC for at least 48 hours duration were evaluated prospectively from November 1997 to October 1998 in the Department of Pediatrics, Shimla showed that the incidence of UTI was 8.4% (11/131). The incidence was 6.1% (5/82) in boys, 12.2% (6/49) in girls, 12.3% (7/57) in infants and 5.4% (4/74) in 13-60 months age group respectively.The incidence of UTI was 33.3% (5/15) among children presenting with urinary symptoms and 4.3% (4/94) in those with ARI. Of the non-urinary symptoms, diarrhea was significantly associated with UTI (4/20) as compared to ARI (4/94) (P <0.05). All four children, (2 boys and 2 girls) with diarrhea and UTI were below 24 months. Conclusion:all acutely febrile children below 5 years with urinary symptoms and those below 24 months with diarrhea should be investigated for UTI.

Murphy CG[33], Two thousand one hundred twenty-eight patients were studied. Among patients categorized as having no signs of

pneumonia (n = 1,084), 5.3% (95% CI = 4.0% to 6.8%) had OP. Presence of cough and longer duration of cough (greater than 10 days) had positive likelihood ratios (LR+) of 1.24 (95% CI = 1.15 to 1.33) and 2.25 (95% CI = 1.21 to 4.20), respectively. Absence of cough had a negative likelihood ratio (LR-) of 0.19 (95% CI = 0.05 to 0.75). The likelihood of occult pneumonia increased with increasing duration of fever (LR+ for more than three days and more than five days of fever, respectively: 1.62; 95% CI = 1.13 to 2.31 and 2.24; 95% CI = 1.35 to 3.71). When obtained (56% of patients), WBC was a predictor of Occult pneumonia, with a LR+ of 1.76 (95% CI = 1.40 to 2.22) and 2.17 (95% CI = 1.58 to 2.96) for WBC of >15,000/mm3 and >20,000/mm3, respectively. Conclusions: Occult pneumonia was found in 5.3% of patients with fever and no lower respiratory tract findings, tachypnea, or respiratory distress. There is limited utility in obtaining a CXR in febrile children without cough. The likelihood of pneumonia increased with longer duration of cough or fever or in the presence of leukocytosis

In a recent study, involving 500 patients leptospirosis was the secondcommon cause of fever contributing to 17%, following malaria which was 27%. Coinfectionof leptospirosis (48 cases) with malaria (220 cases) occurred in 22% ofcases.29 Co-infection of Malaria and Leptospirosis has been reported from Chandigarh [34,35]

Koteeswaran[36] studied samples received between October 2004 and December 2004 (N=2169) indicated that the seroprevalence was found to be more in males (859/1499; 57.30 %) than in females (640/1499; 42.70%). In the age-group analysis, five age groups were made separately for males and females; up to 5 years, 5-10 years, 10-20 years, 20-40 years and above 40 years. The sero positivity distribution for the above groups within positives were 11.41%, 12.11%, 18.16%, 40.16% and 18.16% among male patients and 11.25%, 11.56%, 17.19%, 34.84% and 25.16% among female patients.

Study justification

- Fever without localising sign is more often a diagnostic challenge to treating paeditriacian. 30 % of children with fever presents without localising sign.
- Only very few studies are available in children with FWS in India. Prevalence of serious bacterial infection was not known in our population.
- Most of the guideline in FWS were based on the western studies. This study was conducted to know the etiology of children presenting without localising sign in a tertiary referral centre.

Objectives of the study

To know the aetiology of fever of short duration presenting without localising sign in the age group 1 -36 months.

To know the common organism causing bactremia in our children .

Subjects and Methods

1)Methodology

Study Design : Descriptive study

Place of study: Institute of child health and hospital for Children

Study period: November 2009 to October 2010

Study population: children aged 1 month to 36 months of age

Sample size: 209

Inclusion Criteria: Children presenting with fever of short duration (<7 days) with temperature of more than 38^{o} C and without any localising sign.

Exclusion Criteria:
1. History of antibiotic intake within 48 hrs
2. Children with any immunodeficiency state
3. children with chronic illness

Definitions:

Fever of short duration: Duration of fever for < 7 days

Toxic: A clinical appearance suggestive of serious or critical illness manifest by one or more of the following : some degree of inability, to interact with the parents or guardians, irritability, changes in the degree of consciousness, hypo activity, hypotonia, lethargy, hyper or hypoventilation, hypotension, tachycardia, signs of poor peripheral perfusion or cyanosis.

2) Ethics:

Written informed consent was obtained from the parents and Institution review board clearance was obtained.

3)Maneuver:

- During the study period 837 cases was identified as having fever without localising sign. Among these 209 children who met inclusion and exclusion criteria.
- On admission complaints, history and treatment for present illness, past history, socioeconomic status and immunisation status were recorded in the reliable Informant
- Nutritional status and vitals were recorded.
- A thorough clinical examination was done. Positive findings and relevant negative findings regarding general examination, cardio vascular systems, respiratory systems, gastro intestinal and central nervous system was noted in the proforma.
- blood total count , differential count, Hb, platelet count, peripheral smear , smear for MP, and urine microscopic examination for the presence of pus cells was done in our lab for all patients.
- Blood was taken from a peripheral vein by venepuncture sent for culture in all patients
- Urine was collected by midstream clean catch and urine culture was sent for all patients.
- Lumbar puncture was done in those children who had altered sensorium and seizures.
- Serology for dengue was sent in suspected cases.

- In those children who continued to have fever after 7 days further work up was done to arrive at diagnosis like serology for enteric fever, leptospirosis.
- All the patients with UTI ultrasound examination of the abdomen were done. MCU was done when indicated. All the patients were followed until the final diagnosis was arrived.

Diagnostic criteria

Following criteria was used for establishing diagnosis

Malaria

a. Peripheral smear positive for malarial parasite
b. QBC positivity for malariae

Urinary tract infection.

Any one criteria

a) midstream clean catch urine showing more than 10^5 colonies
b) midstream clean catch urine showing less than 10000 colonies with history of antibiotic taken before culture, high fluid intake, more than 5 leucocytes per high power field in male child or more than 10 leucocytes per high power field in the case of female child

occult Pneumonia : only radiological evidence of pneumonia without any lower respiratory tract sign and symptoms

Bacterial meningitis.

CSF analysis with increased cell count, raised protein, decreased sugar, positive CSF culture or latex agglutination

Leptospirosis:

Microscopic agglutination test showing titre of 1 in 100,or greater in two or more specimen in correlation with clinical symptoms.

Dengue

The World Health Organization criteria for dengue **hemorrhagic fever** are fever (2-7 days in duration or biphasic), minor or major hemorrhagic manifestations, thrombocytopenia ($\leq$100,000/mm^3), and objective evidence of increased capillary permeability (hematocrit increased by $\geq$20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia.

Dengue **shock syndrome** criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure ($\leq$20 mm Hg), and signs of poor perfusion

Unresolved FWS

Those who had self limiting illness and their initial work up is negative is considered as probable viral fever.

Observations

Age and sex distribution of children presenting with fever without focus

Age	1 – 3 months	4 -36 months	Total
Male	26(12.44%)	92(44.02%)	118(56.45%)
Female	20(9.56%)	71(33.97%)	91(43.54%)
Total	46(22%)	163(77.99%)	209(100%)

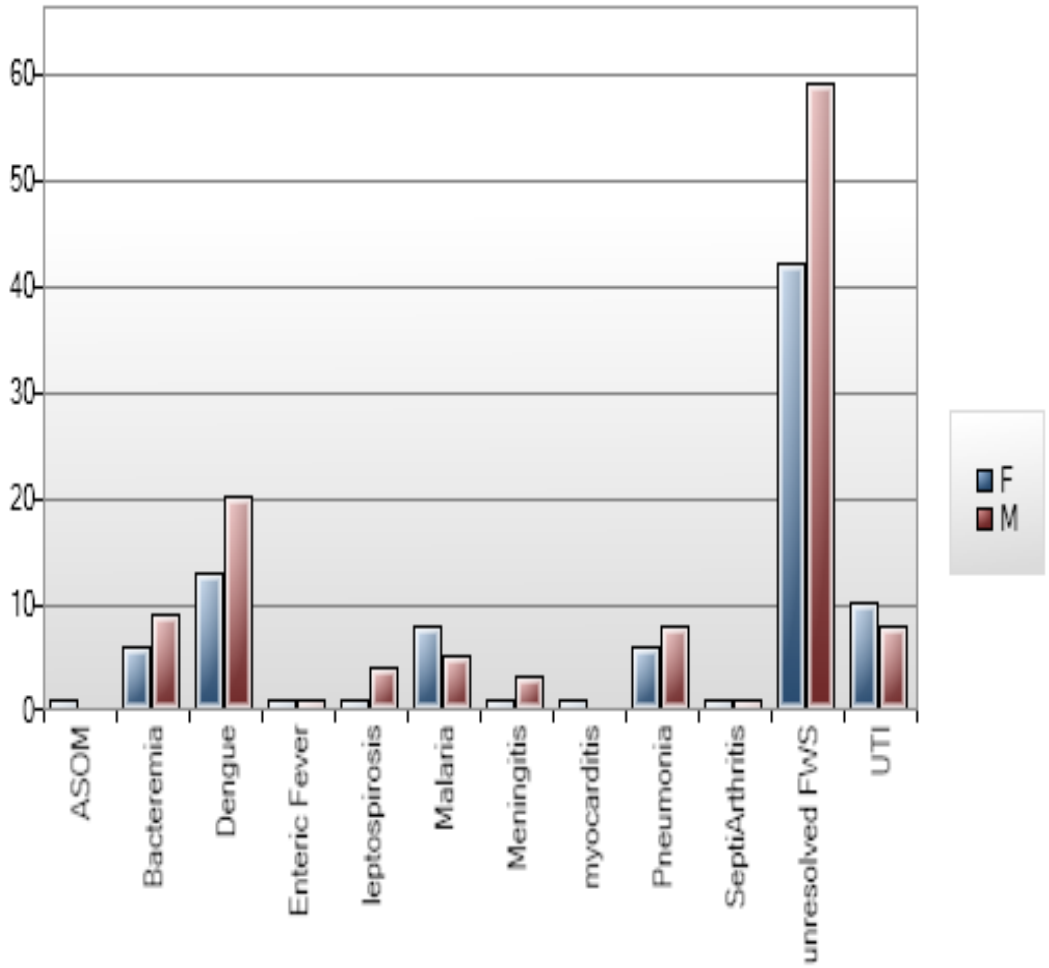
Male to Female to ratio: 1.3:1

Majority of the children were < 1 year old.

Diagnosis and age distribution of children presenting with fever without focus

Age	1 - 3months		4 -36 months		Total	percent
Diagnosis	**No of cases**	**Percent**	**No of cases**	**Percent**		
Abscess	0	0.0%	1	0.61%	1	0.47%
Bacteremia	4	8.69%	11	6.75%	15	7.17%
Dengue	0	0.0%	33	20.24%	33	15.79%
Enteric Fever	0	0.0%	2	1.23%	2	0.96%
Leptospirosis	0	0.0%	5	3.06%	5	2.39%
Malaria	2	4.34%	11	6.75%	13	6.22%
Meningitis	2	4.34%	2	1.23%	4	1.91%
Myocarditis	0	0%	1	0.61%	1	0.47%
Pneumonia	3	6.52%	11	6.75%	14	6.86%
Septic arthritis	1	2.17%	1	0.61%	2	0.96%
UTI	4	8.7%	14	8.59%	18	8.61%
Unresolved FWS	30	65.21%	71	43.55%	101	48.33%
TOTAL	46	100%	163	100%	209	100%

Diagnosis and sex distribution of fever without localising sign



Children with Bacteremia presented as fever without localising sign.

Age	1 – 3 months	4- 36 months	Total
Male	2(13.33%)	7(46.67%)	9(60%)
Female	2(13.33%)	4(26.67%)	6(40%)
Total	4(26.67%)	11(73.33%)	15(100%)

bacteremia was found in 7.17 %. Prevalence of bacteremia is higher in 1- 3 months age group. Empirical antibiotic with ceftriaxone was started on 12 children who are seriously ill.

One among the 15 children had associated pneumonia

10 out 15(66.66) patients showed leukocyte count> 15000/mm^3

Profile of organism isolated from blood culture

Organism	No of isolates (N=15)	1 – 3 months	4 -12 months
Klebsiella	7(46.6%)	2	5
Staphylococcus areus	4(26.6%	2	2
E.coli	2(13.3%)	2	0
Pseudomonas	1(6.6%)	0	1
B haemolytic streptococci	1(6.6%)	1	0

- In klepsiella 5 isolates were sensitive to ciproflaxacin and Amikacin. 1 isolate showed moderate resistance to ciprofloxacin. 3 out of 7 isolates were resistant to cefotaxime. 1 isolate showed resistant to ciprofloxacin, amikacin, cefotoxime but that was sensitive to imipenam.
- In staph.areus 3 were sensitive to cloxacillin, amikacin and vancomicin. One isolate showed resistance to cloxaxacillin but sensitive to vancomycin.
- In E.coli both the isolates were sensitive to cefotaxime and amikacin.

- Pseudomonas showed sensitivity to amikacin and ciprofloxacin
- Beta haemolytic streptococci was sensitive to penicillin, cloxacillin, cefotaxime, and vancomicin.

Children with UTI presented as fever without localising sign.

Age	1 – 3 months	4-36 months	Total
Male	2(11.11%)	6(33.33%)	8(44.44%)
Female	2(11.11%)	8(44.44%)	10(55.56%)
Total	4(22.22%)	14(77.77%)	18(100%)

UTI was the most common infection bacterial infection. Females are more often affected than male children. Children below 3 months of age there is no sex difference. E.coliwas the most the most common organism isolated. All the males were uncircumcised. 2 out of 9 males had associated phimosis.

9 out 18 patients showed WBC > 15000/mm^3

Profile of organism isolated from urine culture

Organism	No of isolates (N=18)	1- 3 months	4-12 months
E.Coli	9(43.47%)	2	6
Klepsiella	7(34.78%)	1	6
Pseudomonas	1(13.04%)	0	1
Proteus	1(8.7%)	0	1

- Most common organism isolated was E.coli. 7 out of 9 isolates were sensitive to ciprofloxacin, amikacin and cefotaxime. 1 was sensitive to ciprofloxacine alone. 1 isolate was resistant to ciprofloxacin and amikacin, cefotaxime but sensitive to imipenam.
- In klepsiella 5 out of 7 isolates were sensitive to ciprofloxacin and amikacin, cefotaxime. 1 out of 7 showed moderate resistance to amikacin. one isolate was sensitive to ciprofloxacin and amikacin
- Pseudomonas showed sensitive to ciprofloxacin and amikacin
- Proteus showed sensitive to ciprofloxacin and amikacin

Children with pneumonia presenting as fever without localising sign.

Age	1 – 3 months	4 -36 months	Total
Male	1(7.14%)	7(50%)	8(57.14%)
Female	2(14.29%)	4(28.57%)	6(42.85%)
Total	3(21.43%)	11(78.57%)	14(100%)

Prevalence of occult pneumonia was same in both the age groups. They presented with fever andnonspecific symptoms like refusal feeds and lethargy. X- ray showed patchy pneumonia in all the patients. All the patients were treated with inj. Ampicillin. All were responded very well.12 out of 15 (80%)patients showed leukocyte count > 15,000/mm^3

Children with malaria presented as fever without localising.

Age	1 – 12 months	25-36 months	Total
Male	1(7.69%)	4(30.76%)	5(38.46%)
Female	1(7.69%)	7(53.85%)	8(61.54%)
Total	2(15.38%)	11(84.61%)	13(100%)

Malaria was found in 4.24% of cases. 12 cases were due to plasmodium vivax and 1 case due to plasmodium falciferum. Peripheral smear for malarial parasite was positive in 10 cases. QBC was positive in about 3 cases. All cases responded well to chloroquine.

Children with meningitis presenting as fever without localising sign

Age	1 – 3 months	4 -36 months	Total
Male	2(50%)	1(25%)	3(75%)
Female	0(0%)	1(25%)	1(25%)
Total	2(50%)	2(50%)	4(100%)

Lumbar puncture was done in those children with irritability and had seizures. In 1 child CSF latex agglutination for hemophilus influenza was positive. In other 3 children diagnosis was made by CSF cytology and biochemistry.

Age sex distribution of children with dengue fever

Age	1 – 3 months	13-36 months	Total
Male	0(0.0)%	20(60.1%)	20(60.61%)
Female	0(0.0%)	13(39.39%)	13(39.39%)
Total	0(0.0%)	33(100%)	33(100%)

Dengue fever was the second most common cause of fever without localising signs. It represented 15.79% of total cases. 25 children recovered without shock. 5 children presented with shock at admission. 3children developed shock and 6 developed petechial rash after admission.

Age and sex distribution of leptospirosis in children presenting with fever without localising sign

Age	1 – 3 months	13 -36 months	Total
Male	0(0%)	4(80%)	4(80%)
Female	0(0%)	1(20%)	1(20%)
Total	0(0%)	4(80%)	5(100%)

3.2% of cases are due to leptospirosis. All the patients were treated with crystalline penicillin. 2 children had enteric fever. Both were treated with inj.ceftrixone. 1 child had ASOM. 2 children had septic arthritis.

Age and sex distribution of unresolved FWS

Age	1 – 3 months	13-36 months	Total
Male	17(16.83%)	42(41.58%)	59(58.41%)
Female	13(12.87%)	29(28.71%)	42(41.58%)
Total	30(29.7%)	71(70.29%)	101(100%)

In about 101 (48.33)patients no focus was identified. Since these children had self limiting illness viral fever was considered as etiology.

20 out of 101 showed WBC count > 15,000/mm^3

Discussion

The present Study was conducted in children who aged between1month to 36 months of age admitted in institute of child health with fever without localising sign. During the study period 837 cases was identified as having fever without localising sign. Among these 209 children who met inclusion and exclusion criteria.

Out of 209 patients 62 patients (29.66%) had serious bacterial infection. In 101(48.33%) patients focus was not identified. Since they had self limiting illness probable viral illness other than dengue was considered. Among the patients with serous bacterial infection UTI was the most common serious bacterial infection which was found in 18(8.61%) cases. Bacteremia was found in 15(7.17%) patients. Other bacterial infection include occult pneumonia in 14 (6.86%) cases, bacterial meningitis in 5 (2.39%), septic arthritis 1n 2 patients(0.96%), leptospirosis in 5(2.39%), enteric fever in 2 (0.96%) patients. Malaria was found in13 cases (6.22%). Dengue was diagnosed in 33 cases (15.79%).

Incidence of serous bacterial infection various quit high (28.2%) in our population compared to western studies[37,38]. In a similar study conducted by Vinchurkar et al[23] in 2002 in 2002 showed serious bacterial infection in 36.2 % of cases.not many studies available in india. Another study conducted by Omolola et al in Nigeria in 2002 showed 39% of bacteremia in 1- 12months age. The epidemiology of bacterial infections

ever changing in children.[39] Bacteremia was found in 12 patients (7.17%). prevalence of bacteremia in children is 5%[18] in 1 -3 months age group. In this study it was 8.69%.

Prevalence bacteremia in 3month – 12 month was 4.9%. Most of the bacteremia was due to gram negative bacteria. Klepsiella was the most common organism isolated. Staph areus was the second most common organism isolated. Study done by Vinchurkar S et all found staph.areus as the most common agent. George O. Akpede, et al[25] in 1992 in Nigeria studied Six-hundred-and-forty-two previously healthy children aged 1 month to 5 years with fever without localizing signs of infection. Their study showed Gram-negative bacteraemia was overall commoner than Grampositivebacteraemia,*Staphylococcus aureus* was the commonest single organism. Study conducted by Omolola et al 1n Nigeria 2002 showed *Escherichia coli* (35.9%), *Staphylococcus aureus*(33.3%). Many western studies[39,40] showed stretocooci pneumonia as most common organism causing bacteremia. In this study no isolate of streptococcus pneumonia was identified

UTI was most common bacterial infection in both the age group. As in other studies females are more commonly affected than males. It was found in 18(8.61%) patients. Prevalence of UTI was same in both the age groups. B. M. Machado et al [21] studied 251 children with fever without localising sign in 2009 in brazil. It showed UTI in 16 cases

(7.4%). R.K. Kaushal et al [32]studied 131 children upto five years of age presenting with fever of >38ºC for from November 1997 to October 1998 in the Department of Pediatrics, IGMC, Shimla showed that the incidence of UTI was 8.4% (). The incidence was 6.1% in boys, 12.2% in girls, 12.3% in infants and 5.4% in 13-60 months age group respectively.The incidence of UTI was 33.3% among children presenting with urinary symptoms and 4.3% in those with ARI.

Robert H. et al[29] studied in U.S, 3066 infants aged 3 months or younger with temperatures of at least 38°C. They found UTI in 5.4% cases. Morris CM[26], Te conducted a prospective study to document the importance of urinary tract infection (UTI) as a cause of fever without a focus (FWF) in children less than 3 years of age. UTI was diagnosed on urine culture in 9(9.2%) of the 98 children. E.coli was the most common organism isolated. Klepsiella was the second most common organism isolated. Most of the isolates were sensitive to amikacin ciproflaxacin

occul Shah[31], studied 1866 patients 308 had no evidence of respiratory distress or lower respiratory tract findings and were studied for Occult pneumonia. Twenty-one patients had Occult pneumonia (6.8%; 95% confidence interval [CI], 4.0%-10.6%). Occult pneumonia was diagnosed in 14 (6.86) % of children which was similar to above study studies.

Bacterial meningitis was found in 4(1.9%) patients. H. infleuenza was the causative organism in 1 patient.in other 3 no osgasm was isolated. Z. Nademi el al studied One hundred and forty one children between 8 days and 16 years of age. They found that 44% of microbiologically proven meningitis and sepsis and 36% of all meningitis and sepsis were meningococcal. Robert H. et al [29]studied in united states 3066 infants aged 3 months or younger with temperatures of at least 38°C. Their study found bacteremia in 1.8% of infants (2.4% of those tested) and bacterial meningitis in 0.5%.

Murphy CG, studied two thousand one hundred twenty-eight patients .Among patients categorized as having no signs of pneumonia 5.3% had occult pneumonia.

Malaria was seen in 13(6.22%) patients. Prevalence malaria increased with increasing age. 12 cases were due to vivax malarae and 1was falciferum malaria infection. George O. Akpede, et al studied Six-hundred-and-forty-two previously healthy children aged 1 month to 5 years with fever without localizing signs of infection.Sixty-three per cent had malaria, 4 per cent bacteraemia, and 7 per cent malaria and bacteraemia. The prevalence of malaria increased with age while that of bacteraemia decreased with age neither infectionwas identified in 27 per cent. Rajnish Joshi et al who studied 1671 patients above 12 yr of age. Malaria was present in 144 (12%) of patients as acute cause of fever.

Sarala rajaji et al from chennai in their study of 75 children has found malaria as the cause of fever in 11 children. Prevalence of malaria in our study is lower than above study

Leptosirosis was found 5 cases (2.39 %). No case was seen in 1to 3month age group Koteeswaran[36] in a large study conducted between 2004 to2006 in tamilnadu showed the sero prevalence of leptospirosis was 11. 41% in under 5 age group. Leptospirosis is an important cause of acute febrile illness. Its incidence and prevalence is increasing in recent years and becoming as global health problem.

Dengue fever was diagnosed in 33(15.79%) patients. There was an epidemic of dengue during the study period. L kapilan et al [42] found dengue in 74.5% (143) of 192 admission with clinical dengue. A considerable proportion of dengue fever (20%) was found in infants of age < 1yr.

Summary

- A prospective study was conducted in children aged 1 month to 36 months of age. 209 children who presented with fever without localising sign were included for the study. Out of 209 patients 118 patients were male 91 were female. In all children relevant investigations were done to identify the focus of the infection.
- Out of 209 patients 62 patients (29.66%) had serious bacterial infection.
- In 100(47.84%) patients focus was not identified. Since they had self limiting illness probable viral illness was considered.
- Among the patients with serous bacterial infection UTI was the most common serious bacterial infection which was found in 18(8.61%) cases. E. Coli was the most common organism isolated. Most of the isolates were sensitive to amikacin and ciprofloxacin.
- Bacteremia was found in 15(7.17%) patients. Klepsiella was the most common organism isolated. Staph. Areus was the second most common organism isolated. Most of the isolates were sensitive to amikacin.
- occult pneumonia in 14 (6.86%) cases. They presented only with fever and non specific symptoms like lethargy and refusal of feeds.

- bacterial meningitis was found in 2.39% of cases. In 1 patient CSF latex agglutination for H.infleunza was positive.
- Other bacterial infections include ,septic arthritis in 2 patients(0.96%)
- Leptospirosis in 5(2.39%), enteric fever in 2 (0.96%) patients.
- Malaria was found in13 patients (6.22%). 11 out of 13 were due to plasmodium vivax. 2 were due to plasmodium falciferum. Al cases responded well to chlroquine.
- Dengue fever was diagnosed in 33 patients (15.79%).

Conclusion

- To conclude serious bacterial was found in 29.66% of cases and UTI was the most common SBI.
- Any child between 1 to 36 months who present with toxic symptoms should be evaluated for the presence serious bacterial infections in the age group of 1 to 36 months.
- Gram negative bacteremia is more common than gram positive.

Limitations of the study:

Study was conducted in a tertiary referral center were mostly sick children are got admitted. Prevalence of bacteremia may not applicable to in children who presents with fever without localising sign in children coming to out patient department.

Recomendations

- Most of the isolates both from urine and blood were susceptible to Amikacin and ciproflaxacin.
- Staphylococcus areus was the second most common organism causing bacteremia. Many isolates were sensitive to amikacin
- Further large scale studies are needed to confirm these findings. Choice of empirical antibiotic in a toxic febrile child without localising sign need to be revised

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Annexure - I

Data collection form

Name:

Age

Study S.No:

Sex:

Address:

Symptoms

Fever: Duration

Character

Chills / Rigor

H/O present illness

Treatment history: prior antibiotic intake yes / no
If yes oral / parenteral duration

H/O Past illness

Diet History

Immunization History

General Examination:

1. Consious 2. Oriented 3. Tachypneic

4. Dyspnoeic. 5. Cyanosis

Temperature

Vitals: Pulse: Respiratory rate:

System Examination:

CVS

RS

Abdomen

CNS

Final Diagnosis

Investigations:

Total WBC count

Differential count

Platelet Count

Peripheral smear

Urine routine

Chest X ray

Urine C&S

Blood C&S

CSF analysis

Others

Annexure - II

Information to Participants

Investigator: Dr Sangeeth S

Name of Participant:

Title: Etiological profile of fever of short duration without focus in children aged 1 month to 36 months

You are invited to take part in this research/ study /procedures. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns. You are being asked to participate in this study being conducted in Institute of Child health and Hospital for children.

What is the Purpose of the Research Febrile infants and children frequently present to primary care and emergency physicians. The majority of these children are younger than 3 years. Most have an apparent source of infection (ie, a viral respiratory infection, acute otitis media, or enteritis). This study aims to find out etiology of fever of short duration without foci
We have obtained permission from the Institutional Ethics Committee.

Study design: Descriptive study

Study Procedures
1. Sick child aged 1 to 36 months who got admitted in ICH with fever of short duration will be enrolled for study
2 Child who present without focus blood culture, urine culture, chest x ray, will be done
3. Further investigation will be done to arrive at diagnosis
Possible risks - Briefly Mention (if any)

Possible benefits to you (if any): Identification of focus of infection

Possible benefits to other people
The result of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

Confidentiality of the information obtained from you
You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and child medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, IEC and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?
Your decisions to not participate in this research study will not affect child's medical care or your relationship with investigator or the institution. Your doctor will still take care of your child and your child will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?
The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during course of the study without giving any reasons. However it is advisable that you talk to the research team prior to stopping the treatment.

INFORMED CONSENT FORM

Study: "Etiological profile of fever of short duration without focus in children aged 1 to 36 months".

Name of the Participant:

Name of the Principal : Dr. Sangeeth S

Name of the Institution: Institute of Child Health and Hospital for Children

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I hereby give my consent to be included as a participant in" **Etiological profile of fever of short duration without focus in children aged 1 to 36 months".**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments given to my child taken in the past _____ months including any native (alternative) treatment
6. I have been advised about the risks associated with my child's participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if my child suffers from unusual symptoms
8. My child has not participated in any research study within the past _____month(s).
9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect future treatment in this hospital.
10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.
11. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
12. I have understand that my child's identity will be kept confidential if my data are publicly presented
13. I have had my questions answered to my satisfaction.
9. I have decided my child to be in the research study.
10. I am aware that if I have any question during this study, I should contact the investigator.

By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Although your child did not or could not give his or her assent, you agree to your child's participation in this study.

Name and Signature of / thumb impression of the participant's parent(s) (or legal representative)

Name _____Signature_____ Date_____

Name _____Signature_____ Date_____

Name and Signature of impartial witness (required for parents of participant child illiterate):

Name _____Signature_____ Date_____

Address and contact number of the impartial witness: _____

Name and Signature of the investigator or his representative obtaining consent:
Name _____Signature_____ Date_____

ஆராய்ச்சி தகவல் தாள்

1. சென்னை எழும்பூர், குழந்தைகள் நல மருத்துவமனையில் 1 முதல் 36 மாதம் வரையிலான மோசமாக உள்ள குழந்தைகளின் காய்சசலுக்கான காரணிகளை கண்டறிதல் பற்றிய ஆய்வு நடைபெறுகின்றது.

2. இந்த ஆராய்ச்சியில் பங்கேற்க தங்களது குழந்தை தேர்வு செய்யப்பட்டுள்ளது.

3. காய்ச்சலுடன் கூடிய மோசமாக உள்ள குழந்தைகளுக்கு ரத்தம், சிறுநீர் மற்றும் இதர பரிசோதனைகள் செய்து காய்ச்சலுக்கான காரணங்கள் கண்டறியப்படுகின்றது. இதனால் தங்களது குழந்தைக்கு எந்தவித பாதிப்பும் ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம.

4. முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது குழந்தையின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

5. இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் இந்த ஆராய்ச்சிலிருந்து எந்த நேரமும். பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

6. இந்த பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போதோ அல்லது ஆராய்ச்சியின் முடிவின் போதோ தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் பெற்றோர் / காப்பாளர் கையொப்பம்

தேதி

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு : 1 முதல் 36 மாதம் வரையிலான மோசமாக உள்ள குழந்தைகளின் காய்ச்சலுக்கான காரணிகளை கண்டறிதல்

பெயர் : தேதி :

வயது : உள்நோயாளி எண் :

பால் : ஆராய்ச்சி சேர்க்கை எண் :

1. இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.
2. எனக்கு விளக்கப்பட்ட விசயங்களை நான் புரிந்து கொண்டு நான் எனது குழந்தை இந்த ஆராய்ச்சியில் பங்கேற்க எனது முழு மனதுடன் சம்மதிக்கிறேன்.
3. இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி எனது சொந்த விருப்பத்தின் பேரில் எனது குழந்தை பங்கேற்க சம்மதிக்கிறேன்.
4. இந்த ஆராய்ச்சியிலிருந்து எந்த நேரமும் பின்வாங்கலாம் என்பதையும், அதனால் சிகிச்சையில் எந்த பாதிப்பும் ஏற்படாது என்பதையும் அறிந்து கொண்டேன்.
5. நான் இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல் தாளை பெற்றுக் கொண்டேன்.
6. நான் என்னுடைய சுயநினைவுடனும் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் எனது குழந்தை பங்கேற்க சம்மதிக்கிறேன்.
7. எனது குழந்தைக்கு இரத்த மற்றும் இதர பரிசோதனை செய்து கொள்ள முழு மனதுடன் சம்மதிக்கிறேன்.

பெற்றோர் / காப்பாளர் கையொப்பம்

Abbrevations

CBC	Complete blood count
CI	Confidence interval
CSF	Cerebrospinal fluid
FWS	Fever without localising sign
HPF	High-powered field
LR	Likelihood ratio
RBC	Red blood cell
UTI	Urinarytract infection
WBC	White blood cell